US005849780A

United States Patent [19]

Di Malta et al.

[11] Patent Number: 5,849,780

[45] Date of Patent: Dec. 15, 1998

[54] **1-BENZENESULFONYL-1-1,3-DIHYDROINDOL-2-ONE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT**

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[21] Appl. No.: **323,921**

[22] Filed: **Oct. 17, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 129,310, Sep. 30, 1993, abandoned.

[30] **Foreign Application Priority Data**

Jan. 30, 1992	[FR]	France	92 01034
Jul. 30, 1993	[FR]	France	93 09404
Jul. 28, 1994	[EP]	European Pat. Off.	94 401 737.5

[51] **Int. Cl.**[6] **A61K 31/40**; A61K 31/44; C07D 209/34; C07D 209/96

[52] **U.S. Cl.** **514/409**; 540/602; 544/62; 544/144; 544/373; 546/17; 546/187; 546/201; 546/256; 546/277.7; 548/410; 548/411; 548/486; 548/487; 562/833

[58] **Field of Search** 548/411; 514/409; 540/602; 544/62, 144, 373; 546/187, 201, 256, 277.7

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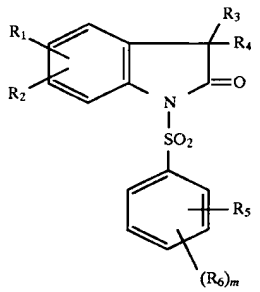
[57] **ABSTRACT**

The invention relates to 1-Benzenesulfonyl-1,3-dihydroindol-2-one derivatives of the formula



(I)

and their salts, where appropriate, to their preparation and to pharmaceutical compositions in which they are present. These compounds have an affinity for the vasopressin and/or ocytocin receptors.

31 Claims, No Drawings

DCM is stirred for 2 hours at RT. 40 ml of a saturated solution of $NaHCO_3$ are added, the mixture is decanted, the organic phase is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/MeOH mixture (90/10; v/v) as the eluent to give the expected product.

M.p.=109° C.

EXAMPLE 355

5-Ethoxy-1-[4-(N',N'-diethylureido)-2-methoxybenzenesulfonyl]-1,3-dihydro-3-spiro(4-formyloxycyclohexane)indol-2-one, the More Polar Isomer

A mixture of 0.25 g of the compound obtained in EXAMPLE 343, 0.18 g of cesium carbonate, 0.45 ml of dimethyl sulfate and 12 ml of DMF is heated at 40° C. for 12 hours. 10 ml of water are added, the reaction mix ture is extracted with AcOEt, the organic phase is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using DCM as the eluent to give 0.2 g of the expected product after recrystallization from a cyclohexane/AcOEt mixture.

M.p.=155° C.

EXAMPLE 356

5-Ethoxy-1-[4-(N',N'-diethylureido)-2-methoxybenzenesulfonyl]-1,3-dihydro-3-spiro(4-acetoxycyclohexane)indol-2-one, the More Polar Isomer

A mixture of 3 g of the compound obtained in EXAMPLE 343, 0.75 g of 4-dimethylaminopyridine, 3 ml of acetic anhydride and 5 ml of DCM is heated at 40° C. for 5 hours. Water is added to the reaction mixture, ex traction is carried out with DCM, the extract is washed with water and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/cyclohexane mixture as the eluent to give the expected product after recrystallization from iso ether.

M.p.=140° C.

EXAMPLE 357

5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-dihydroxytricyclo[5.2.1.$0^{2,6}$]-decan-4-yl)indol-2-one

A) 5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-epoxytricyclo[5.2.1.$0^{2,6}$]decan-4-yl)indol-2-one

A mixture of 0.3 g of 5-ethoxy-1,3-dihydro- 1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(tricyclo-[5.2.1.$0^{2,6}$]dec-8-en-4-yl)indol-2-one and 0.2 g of metachloroperbenzoic acid in 20 ml of DCM is stirred for 3 hours at RT. 15 ml of a saturated solution of $NaHCO_3$ are added, the mixture is decanted, extraction is carried out with DCM, the extract is dried over mag nesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using DCM as the eluent to give 0.25 g of the expected product after recrystallization from an acetone/DCM mixture.

M.p.=263° C.

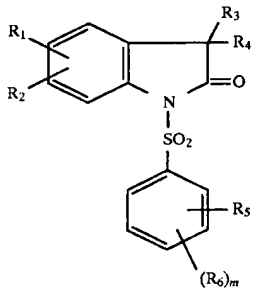
B) 5-Ethoxy-1,3-dihydro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiro(8,9-dihydroxytricyclo[5.2.1.$0^{2,6}$]decan-4-yl)indol-2-one

A mixture of 0.2 g of the compound obtained in the previous step, 20 ml of water, 2 ml of concentrated sulfuric acid and 20 ml of THF is refluxed for 8 hours. The reaction mixture is neutralized by the addition of a saturated solution of $NaHCO_3$, the solvent is evaporated off under vacuum, the residue is extracted with DCM and dried over magnesium sulfate and the solvent is evaporated off under vacuum. The residue is chromatographed on silica using a DCM/MeOH mixture (99/1; v/v) as the eluent to give 0.17 g of the expected product.

M.p.=150° C.

What is claimed is:

1. A compound of formula



(I)

in which

R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1–C_7-ω-halogenoalkoxy, a halogen, a C_1–C_7-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a C_1–C_7-polyhalogenoalkoxy, a C_2–C_7-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C_2–C_7, a C_2–C_7-ω-aminoalkoxy which is free or substituted by one or two C_1–C_7-alkyls; a C_3–C_7-cycloalkoxy; a cycloalkyl methoxy in which the cycloalkyl is C_3–C_7; a phenoxy; a benzyloxy; a C_1–C_7-alkylthio; a phenylthio; a nitro; an amino which is free or substituted by one or two C_1–C_7-alkyls; a cyano; a C_1–C_7-acyl; a C_1–C_7-acyloxy; a C_1–C_7-alkylsulfonamido; a phenylsulfonamido; a benzylsulfonamido; a C_1–C_7-alkylamido; a C_1–C_7-alkoxycarbonylamino; a ureido which is unsubstituted or substituted by a phenyl, by a benzyl or by one or two C_1–C_7-alkyls; or a thioureido which is unsubstituted or substituted by a phenyl, by a benzyl or by one or two C_1–C_7-alkyls;

R_3 and R_4, together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated C_3–C_{12} hydrocarbon ring which is unsubstituted or substituted by one or more C_1–C_7-alkyl groups, by an oxo group, by a C_3–C_5-spirocycloalkyl or by a hydroxy which is free or substituted by a group selected from the group consisting of C_1–C_4-alkyl groups, C_1–C_2-alkoxyalkyl groups in which the alkyl is C_1–C_4, phenylalkoxyalkyl groups in which the alkoxy is C_1–C_2 and the alkyl is C_1–C_4, and tetrahydrofuranyl and tetrahydropyranyl groups; or else

R_5 and R_6 are each independently a hydrogen, a halogen, a C_1–C_7-alkyls, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C_1–C_7-alkyl; a hydroxyamino; a hydroxy; a carboxy; a guanidino which is unsubstituted or mono-substituted or disubstituted by a C_1–C_7-alkyl, a phenyl or a benzyl; a group OR_7; a group SR_7; a C_1–C_7-acyl; a C_1–C_7-alkoxycarbonyl; a phenoxycarbonyl; a benzyloxycarbonyl; a carbamoyl substituted by groups R'_6 and R''_6; a thiocarbamoyl which is free or substituted by one or two C_1–C_7-alkyls; a sulfamoyl; an alkylsulfamoyl or

dialkylsulfamoyl in which the alkyl is C_1–C_7; a group $SO_2R'_7$; an alkylsulfonamido in which the alkyl is C_1–C_7; a phenylsulfonamido; a benzylsulfonamido; a group COR'_7; a group NR_8R_9 or a group CO—NH—$CR_{10}R'_{10}$—COR_{12}; the phenyl group forming part of the substituent R_5 and/or R_6 can be unsubstituted or monosubstituted or polysubstituted by a C_1–C_7-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is C_1–C_7, a carboxy, an alkoxycarbonyl in which the alkyl is C_1–C_7, a C_1–C_7-acyloxy or an imidazolyl;

R'_6 and R''_6 are each independently hydrogen, a C_1–C_7-alkyl which is unsubstituted or substituted by one or more halogens or by R'''_6; a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl or a methylpiperidin-4-yl; or $R\alpha_6$ and R''_6 form, with the nitrogen atom to which they are bonded, a pyrrolidino group which is unsubstituted or substituted by a hydroxymethyl or by a carbamoyl which is free or substituted by one or two C_1–C_7-alkyls;

R'''_6 is a hydroxy; a C_1–C_7-alkoxy; an amino which is free or substituted by one or two C_1–C_7-alkyls; a carbamoyl which is free or substituted by one or two C_1–C_7-alkyls or in which the two substituents, together with the nitrogen atom to which they are bonded, form a pyrrolidino, a piperidino or an azepino; a cyano; a carboxy which is free or esterified by a C_1–C_7-alkyl or by a benzyl; a phenyl; a C_3–C_7-cycloalkyl; an adamantyl or a heterocyclic radical selected from pyridyl, methylpyridyl, furanyl, tetrahydrofuranyl, thienyl, methylthienyl, pyrrolidino, piperidino and azepino groups;

R_7 is a C_1–C_7- alkyl, a phenyl, a benzyl, a C_3–C_7-cycloalkyl, a C_2–C_7-alkenyl, a C_1–C_7-ω-halogenoalkyl, a C_1–C_7-polyhalogenoalkyl, a C_1–C_7-acyl, a C_1–C_7-ω-carboxyalkyl which is free or esterified by a C_1–C_7-alkyl or by a benzyl; a C_2–C_7-ω-aminoalkyl in which the amino group is free, substituted by one or two C_1–C_7-alkyls or in the form of an ammonium ion with a physiologically acceptable anion; or a C_1–C_7-ω-carbamoylalkyl which is free or substituted by one or two C_1–C_7-alkyls;

R'_7 is a piperazin-1-yl group which is unsubstituted or substituted in the 4-position by a group R''_7; a piperidino group which is unsubstituted or substituted in the 4-position by a group R'''_7; an azetidin-1-yl group which is unsubstituted or substituted in the 3-position by a group R'''_7; a pyridyl group which is unsubstituted or substituted by a methyl; or a pyrrolidino group which is substituted by a group R''''_7;

R''_7 is a C_1–C_7-alkyl, a phenyl, a benzyl or a C_1–C_7-acyl;

R'''_7 is R''_7 or an amino which is free or carries a protecting group;

R''''_7 is R'''_7 or a carboxy group which is free or esterified by a C_1–C_7-alkyl;

R_8 and R_9 are each independently a hydrogen, a C_1–C_7-alkyl or a benzyl; R_9 can also be a C_3–C_8-alkene in which the double bond is in the C_3–C_4-position; a C_1–C_7-acyl; a C_1–C_7-thioacyl; a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7; a cycloalkylthiocarbonyl in which the cycloalkyl is C_3–C_7; a C_1–C_7-ω-aminoacyl; a C_1–C_7-ω-hydroxyacyl; a C_1–C_7-ω-benzyl-oxyacyl; a phenoxycarbonyl; a thienocarbonyl a pyridylcarbonyl; a methylpyridylcarbonyl; a C_1–C_7-alkoxycarbonyl; a benzoyl; a phenacetyl; a group CO—$CR_{10}R'_{10}$-$NR_{11}R'_{11}$; a group $CR_{10}R'_{10}COR_{12}$; a group $(CH_2)_tCOR_{12}$; a group $CO(CH_2)_{t'}COR_{12}$; a carbamoyl which is unsubstituted or substituted by R_{14} and R'_{14}; a thiocarbamoyl which is unsubstituted or substituted by R_{14} and R'_{14}; or a heterocyclic radical selected from pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridazinyl, pyrimidinyl, pyridyl and thiazolyl groups; or

R_8 and R_9, together with the nitrogen atom to which they are bonded, form hydantoin, N-methylhydantoin or a heterocycle selected from the group consisting of pyrrole, dihydropyrrole, pyrrolidine and isoindole, in which the benzene ring can be unsubstituted or substituted by a halogen, a C_1–C_7-alkyl, a trifluoromethyl or a methoxy;

R_{10} and R'_{10} are each independently hydrogen, a C_1–C_7-alkyl or a benzyl, or R_{10} and R'_{10}, together with the carbon atom to which they are bonded, form a C_3–C_7-cycloalkyl;

R_{11} and R'_{11} are each independently hydrogen or a C_1–C_7-alkyl;

R_{12} and a hydroxy, a C_1–C_7-alkoxy or an amino which is unsubstituted or substituted by one or two C_1–C_7-alkyls;

R_{14} and R'_{14} are each independently a C_1–C_7-alkyl which is unsubstituted or substituted by R_{15}, a phenyl which is unsubstituted or substituted by R'_{15}, a C_3–C_7-cycloalkyl or an adamantyl; or

R_{14} and R'_{14}, together with the nitrogen atom to which they are bonded, form a heterocycle selected from morpholine, thiomorpholine, piperazine, azetidine, pyrrolidine, piperidine and azepine, said heterocycle being unsubstituted or substituted by one or more methyl groups, by a phenyl or by an amino group which is free or carries a protecting group;

R_{15} is a phenyl, a pyridyl, a hydroxy, a C_1–C_7-alkoxy, an amino which is free or substituted by one or two C_1–C_7-alkyls, or a carboxy which is free or esterified by a C_1–C_7-alkyl;

R'_{15} is a hydroxy or an amino which is free or substituted by one or two C_1–C_7-alkyls;

m is 1 or, if R_6 is a halogen, a C_1–C_7-alkyl or a C_1–C_7-alkoxy, m can also be 2, 3 or 4, or else $(R_6)_m$ can be m substituents having different meanings selected from halogen, C_1–C_7-alkyl and C_1–C_7-alkoxy;

t is an integer which can vary from 2 to 5;

t' is an integer which can vary from 1 to 5;

and its salts.

2. A compound according to claim **1**, wherein R_1 is in the 5-position of the indole and R_2 is hydrogen.

3. A compound according to claim **1**, wherein R_1 is a chlorine or fluorine atom or an ethoxy group in the 5-position of the indole and R_2 is hydrogen.

4. A compound according to claim **1**, wherein R_3 and R_4, together with the carbon to which they are bonded, form a C_3–C_{12}-hydrocarbon ring.

5. A compound according to claim **1**, wherein R_3 and R_4, together with the carbon to which they are bonded, form a cycloheptane, an adamantane, a tricyclo[5.2.1.$0^{2,6}$]dec-8-ene, a bicyclo[2.2.1]heptane, a bicyclo[3.3.1]nonane or a cyclohexane which is unsubstituted or substituted by a C_3–C_5-spirocycloalkyl or by one or two C_1—C_7-alkyl groups.

6. A compound according to claim **1**, wherein the substituents R_5 and R_6 are respectively in the 2- and 4-positions.

7. A compound according to claim **6**, in which R_5 and R_6 are each a methoxy.

8. A compound according to claim 1, in which R_5 in the 2-position is a methoxy and R_6 in the 4-position is C_1–C_7-acylamino, a C_1–C_4-dialkylureido or an alkoxycarbonylalkylcarbamoyl in which the alkyl groups are C_1–C_7.

9. A compound according to claim 1, wherein R_5 is an orthomethoxy group and R_6 in the para-position is a group selected from the group consisting of:

piperidin-1-yl-carbonylamino,

(2-cyanoprop-2-yl)carbonyl,

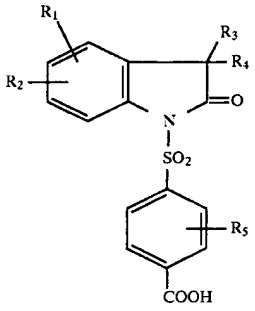
pyrrolidin-1-yl,

N,N-diethylguanidino and

N,N-diethylthioureido.

10. A compound according to claim 1, of the formula:

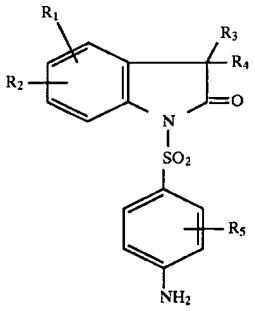
(IX)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1, and said compound including pharmaceutically acceptable esters of the carboxyl group.

11. A compound according to claim 1, of the formula:

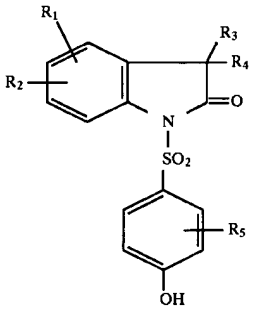
(X)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1, and its salts where appropriate.

12. A compound according to claim 1, of the formula:

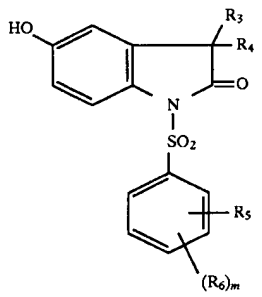
(XI)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1.

13. A compound according to claim 1, of the formula:

(XII)



in which R_3, R_4, R_5 and R_6 and m are defined as indicated above for (I) in claim 1.

14. A pharmaceutical composition which contains a compound according to any one of claims 1 to 13 in combination with a pharmaceutically acceptable carrier or excipient.

15. A compound of formula (I) according to claim 1, in which

R_1 and R_2 are each independently a hydrogen, a hydroxyl, a C_1–C_4-ω-halogenoalkoxy, a halogen, a C_1–C_4-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a C_1–C_4-polyhalogenoalkoxy, a C_2–C_4-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4-ω-aminoalkoxy which is free or substituted by one or two C_1–C_4 alkyl groups, a C_3–C_7-cycloalkyloxy, a cycloalkylmethoxy in which the cycloalkyl is a C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4-alkythio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4-alkyl groups, a cyano, a C_1–C_4-acyl, a C_1–C_4-acyloxy, a C_1–C_4-alkylsulfonamido, a phenylsulfonamido, a C_1–C_4-alkylamido, a C_1–C_4-alkoxycarbonylamino, a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4-alkyl groups;

R_3 and R_4 together with the carbon atom to which they are bonded form an optionally fused, saturated or unsaturated C_3–C_{10} hydrocarbon ring, which is unsubstituted or substituted by one or more C_1–C_7-alkyl groups or by a C_3–C_5-spirocycloalkyl;

or else

R_5 and R_6 are each independently hydrogen, a halogen, a C_1–C_7-alkyl, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C_1–C_7-alkyl groups, a hydroxy amino, a hydroxy, a carboxy, a group OR_7, a group SR_7, a C_1–C_7-acyl, a C_1–C_7-alkoxycarbonyl, a phenoxycarbonyl, a benzyloxycarbonyl, a carbamoyl which is substituted by R'_6 and R''_6 groups, a thiocarbamoyl which is free or substituted by one or two C_1–C_7-alkyl groups, a sulfamoyl, an alkylsulfamoyl or a dialkylsulfamoyl in which the alkyl is C_1–C_7, a $SO_2R'_7$ group, an alkylsulfonamido in which the alkyl is C_1–C_7, a group COR'_7, a group NR_8R_9, a CO—NH—$CH(R_{10})$—COR_{12} group; the phenyl group forming part of the substituent R_5 and/or R_6 can be unsubstituted or substituted one or more times by a C_1–C_7-alkyl, a trifluoromethyl, a methoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is C_1–C_7, a carboxy, a C_1–C_7-alkoxycarbonyl, a C_1–C_7-acyloxy, an imidazolyl;

R'_6 and R''_6 are each independently hydrogen, a C_1–C_7-alkyl which is unsubstituted or substituted by R'''_6, a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl, a methylpiperidin-4-yl, or else R'_6 and R''_6, together with the nitrogen atom to which they are connected, form a heterocycle selected from piperazine and piperidine;

R'''_6 is a hydroxyl, a cyano, a carboxy which is free or esterified by a C_1–C_7-alkyl or by a benzyl, a phenyl, a pyridyl, a methylpyridyl, an amino which is free or substituted by one or two C_1–C_7-alkyl groups;

R_7 is a C_1–C_7-alkyl, a phenyl, a benzyl, a C_3–C_7-cycloalkyl, a C_2–C_4-alkenyl, a C_1–C_7-ω-halogenoalkyl, a C_1–C_7-polyhalogenoalkyl, a C_1–C_7-acyl, a C_1–C_7-ω-carboxyalkyl which is free or esterified by a C_1–C_4-alkyl group or by a benzyl, a C_2–C_7-ω-aminoalkyl in which the amino group is free or substituted by one or two C_1–C_4-alkyl groups or in the form of an ammonium ion with a physiologically acceptable anion;

R'_7 is a piperazin-1-yl group which is unsubstituted or substituted in the 4-position by a group R''_7, a piperidino group which is unsubstituted or substituted in the 4-position by a group R'''_7, an azetidin-1-yl group which is unsubstituted or substituted in the 3-position by a group R'''_7, a pyridyl group which is unsubstituted or substituted by a methyl;

R''_7 is a C_1–C_4-alkyl, a phenyl, a benzyl, a C_1–C_4-acyl;

R'''_7 is R''_7 or an amino which is free or carries a protecting group;

R_8 and R_9 are each independently hydrogen, a C_1–C_7-alkyl, a phenyl, a benzyl; R_9 may also be a C_1–C_7-acyl, a C_1–C_7-thioalkyl, a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7, a cycloalkylthiocarbonyl in which the cykloalkyl is C_3–C_7, a C_1–C_4-ω-aminoacyl, a C_1–C_4-ω-hydroxyacyl, a C_1–C_4-ω-benzyloxyacyl, a phenoxycarbonyl, a thienocarbonyl, a pyridylcarbonyl, a methylpyridylcarbonyl, a C_1–C_4-alkoxycarbonyl, a benzoyl, a group —CO—$CH(R_{10})$—$NR_{11}R'_{11}$, a group —$CH(R_{10})$—CO_2R_{11}, a group $(CH_2)_tCOR_{12}$, a group $CO(CH_2)_tCOR_{12}$, a carbamoyl which is unsubstituted or substituted by a phenyl or by one or two C_2–C_4-alkyl groups;

m is 1 or, when R_6 is halogen, a C_1–C_7-alkyl or a C_1–C_7-alkoxy, m can also be 2, 3 or 4 or else $(R_6)_m$ can represent m substituents having different meanings selected from halogen, a C_1–C_7-alkyl or a C_1–C_7-alkoxy;

R_{10} is hydrogen, a C_1–C_4-alkyl or a benzyl;

R_{11} and R'_{11} are each independently hydrogen or a C_1–C_4 alkyl;

R_{12} is a hydroxyl, a C_1–C_4-alkoxy or an amino which is unsubstituted or substituted by one or two C_1–C_4-alkyl groups;

t is an integer varying from 1 to 5;

as well as its possible salts.

16. A compound of formula (I) according to claim **15**, in which R_1 is chlorine or an ethoxy group in the 5-position of the indole ring and R_2 is hydrogen.

17. A compound of formula (I) according to claim **15**, in which R_3 and R_4 together with the carbon atom to which they are bonded form a C_3–C_{10}-hydrocarbon ring.

18. A compound of formula (I) according to claim **15**, in which R_3 and R_4 together with the carbon atom to which they are bonded form a cyclohexane which is unsubstituted or substituted by one or two C_1–C_7-alkyl groups or by a C_3–C_5-spirocycloalkyl; a cycloheptane, an adamantane or a tricyclo[5.2.1.$0^{2,6}$]dec-8-ene.

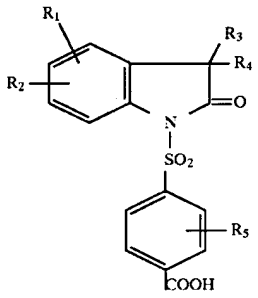
19. A compound of formula (I) according to claim **15**, in which R_5 and R_6 are each a methoxy.

20. A compound of formula (I) according to claim **15**, in which R_5 in the 2-position is a methoxy group and R_6 in the 4-position is a C_1–C_7-acylamino, a C_1–C_4-dialkylureido, an alkoxycarbonylalkylcarbamoyl in which the alkyl groups are C_1–C_7.

21. A compound of formula (I) according to claim **15**, in which R_1 is in the 5-position and R_2 is hydrogen.

22. A compound according to claim **15** of formula:

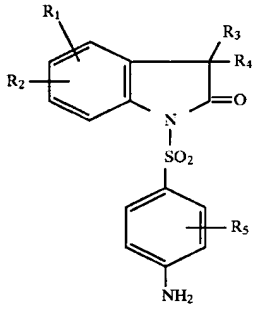
(IX)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim **15** and its functional derivatives.

23. A compound according to claim **15**, of formula:

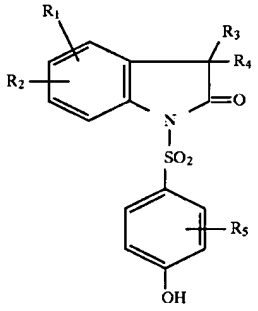
(X)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim **15**, and its possible salts.

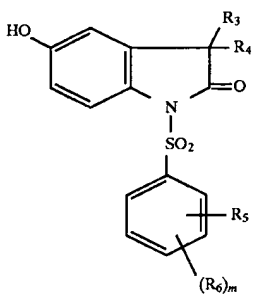
24. A compound according to claim **15** of formula:

(XI)



in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim **15**.

25. A compound according to claim 15 of formula:

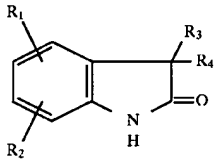


(XII)

in which R_3, R_4, R_5 and R_6 are defined as indicated above for (I) in claim 15.

26. A pharmaceutical composition containing as active principle a compound according to any one of claims 15 to 21.

27. A compound of the formula:



(II)'

in which

R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1–C_4-ω-halogenoalkoxy, a halogen, a C_1–C_4-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a C_1–C_4-polyhalogenoalkoxy, a C_2–C_4-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4-ω-aminoalkoxy which is free or substituted by one or two C_1–C_4-alkyls, a C_3–C_7-cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4-alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4-alkyls, a cyano, a C_1–C_4-acyl, a C_1–C_4-acyloxy, a C_1–C_4-alkylsulfonamido, a phenylsulfonamido, a C_1–C_4-alkylamido, a C_1–C_4-alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4-alkyls; and

R_3 and R_4, together with the carbon to which they are bonded, form

an adamantane,

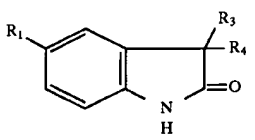
an indane or a hexahydroindane which are unsubstituted or substituted by one or more C_1–C_7-alkyl groups,

a tricyclo[5.2.1.$0^{2,6}$]decane or a tricyclo[5.2.1.$0^{2,6}$]dec-8-ene which are unsubstituted or substituted by one or more C_1–C_7-alkyl groups, or

a C_4–C_8-hydrocarbon ring substituted by one or more C_1–C_7-alkyl groups or by a C_3–C_5-spirocyclo-alkyl;

with the limitation that if CR_3R_4 is adamantane, R_1 and R_2 are other than hydrogen.

28. A compound of the formula:



(II)"

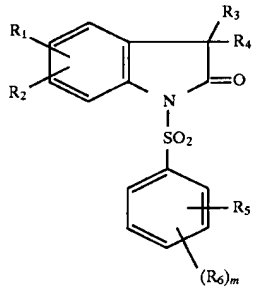
in which

R_1 is a hydroxy, a C_1–C_4-ω-halogenoalkoxy, a halogen, a C_1–C_4-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a C_1–C_4-polyhalogenoalkoxy, a C_2–C_4-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C_2–C_4, a C_1–C_4-ω-aminoalkoxy which is free or substituted by one or two C_1–C_4-alkyls, a C_3–C_7-cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4-alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4-alkyls, a cyano, a C_1–C_4-acyl, a C_1–C_4-acyloxy, a C_1–C_4-alkylsulfonamido, a phenylsulfonamido, a C_1–C_4-alkylamido, a C_1–C_4-alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4-aklyls;

R_3 and R_4, together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated C_3–C_{10}-hydrocarbon ring which is unsubstituted or substituted by one or more C_1–C_7-alkyl groups or by a C_3–C_5-spirocycloalkyl.

29. A compound according to claim 28 in which R_1 is ethoxy.

30. A compound of the formula



(I)

in which

R_1 and R_2 are each independently a hydrogen, a hydroxy, a halogen, a C_1–C_7-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a C_2–C_7-ω-hydroxyalkoxy, a C_2–C_7-ω-aminoalkoxy which is free or substituted by one or two C_1–C_7-alkyls; a C_3–C_7-cycloalkoxy; a cycloalkyl methoxy in which the cycloalkyl is C_3–C_7; a phenoxy, a benzyloxy; a C_1–C_7 alkylthio; a nitro; an amino which is free or substituted by one or two C_1–C_7-alkyls; a cyano; a C_1–C_7-acyl; C_1–C_7-acyloxy; a C_1–C_7-alkylamido; a ureido which is unsubstituted or substituted by a phenyl, by a benzyl or by one or two C_1–C_7-alkyls;

R_3 and R_4, together with the carbon to which they are bonded, form a cyclopentane, a cycloheptane, a tetrahydrofuran, an adamantane, a tricyclo-[5.2.1.$0^{2,6}$] dec-8-ene, a bicyclo[2.2.1]heptane, a bicyclo[3.3.1]nonane or a cyclohexane which is unsubstituted or substituted by a C_3–C_5-spirocycloalkyl or by one or two C_1–C_7-alkyl groups,

R_5 and R_6 are each independently a hydrogen, a halogen, a C_1–C_7-alkyl, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C_1–C_7-alkyls; a hydroxy; a carboxy; a group OR_7; (C_1–C_4)alkylthio; a C_1–C_7-acyl; a C_1–C_7-alkoxycarbonyl; a phenoxycarbonyl; a benzyloxycarbonyl; a carbamoyl substituted by groups R'_6 and R''_6; a thiocarbamoyl which is free or substituted by one or two C_1–C_7-alkyls; a sulfamoyl; a group $SO_2R'_7$; an alkylsulfonamido in which the alkyl is C_1–C_7; a phenylsulfonamido; a benzylsulfonamido; a group COR'_7;

a group NR_8R_9 or a group CO—NH—CR_{10}—$R'_{10}COR_{12}$; the phenyl group forming part of the substituent R_5 and/or R_6 can be unsubstituted or monosubstituted or polysubstituted by a C_1–C_7-alkyl, a trifluoromethyl, a C_1–C_7-alkoxy, a halogen, a sulfamoyl, a carboxy or an imidazolyl;

R'_6 and R''_6 are each independently hydrogen, a C_1–C_7-alkyl which is unsubstituted or substituted by one or more halogens or by R'''_6; a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl or a methylpiperidin-4-yl;

R'''_6 is a hydroxy; a C_1–C_7-alkoxy; a carboxy which is free or esterified by a C_1–C_7-alkyl or by a benzyl;

R_7 is a C_1–C_7-alkyl, a phenyl, a benzyl, a C_1–C_7-ω-halogenoalkyl, a C_1–C_7-polyhalogenoalkyl, a C_1–C_7-acyl, a C_1–C_7-ω-carboxyalkyl which is free or esterified by a C_1–C_7-alkyl; a C_2–C_7-ω-aminoalkyl in which the amino group is free, substituted by one or two C_1–C_7-alkyls, or in the form of an ammonium ion with a physiologically acceptable anion; or a C_1–C_7-ω-carbamoylalkyl which is free or substituted by one or two C_1–C_7-alkyls;

R'_7 is a piperazine-1-yl group which is unsubstituted or substituted in the 4-position by a group R''_7;

R''_7 is a C_1–C_7-alkyl;

R'''_7 is an amino which is free or carries a protecting group;

R''''_7 is R'''_7 or a carboxy group which is free or esterified by a C_1–C_7-alkyl;

R_8 and R_9 are each independently a hydrogen, a C_1–C_7-alkyl or a benzyl; R_9 can also be a C_1–C_7-acyl; a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7; a cycloalkylthio-carbonyl in which the cycloalkyl is C_3–C_7; a C_1–C_7-ω-aminoacyl; a C_1–C_7-ω-benzyloxyacyl; a phenoxycarbonyl; a thienocarbonyl; a benzoyl; a phenacetyl; a carbamoyl which is unsubstituted or substituted by a phenyl or one or two C_1–C_4 alkyls;

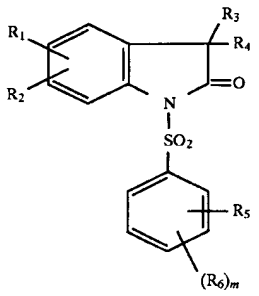
R_{10} and R'_{10} are each independently hydrogen, a C_1–C_7-alkyl or a benzyl, or R_{10} and R'_{10}, together with the carbon atom to which they are bonded, form a C_3–C_7-cycloalkyl;

R_{11} and R'_{11} are each independently hydrogen or a C_1–C_7-alkyl;

R_{12} is a hydroxy, a C_1–C_7-alkoxy or an amino which is unsubstituted or substituted by one or two C_1–C_7-alkyls;

m is 1 or, if R_6 is a halogen, a C_1–C_7-alkyl or a C_1–C_7-alkoxy, m can also be 2, 3 or 4, and its salts.

31. A compound of the formula



(I)

in which

R_1 is a halogen or a (C_1–C_7)alkoxy;

R_2 is hydrogen;

R_3 and R_4, together with the carbon to which they are bonded, form a cyclohexane which is unsubstituted or substituted by one or two C_1–C_7-alkyl groups;

R_5 is hydrogen or a group OR_7;

R_6 is a group OR_7, a carbamoyl substituted by groups R'_6 and R''_6 or a group NR_8R_9;

R'_6 and R''_6 are each independently hydrogen, a C_1–C_7-alkyl which is unsubstituted or substituted by one or more halogens or by R'''_6; a phenyl, a pyridyl, a methylpyridyl, a piperidin4-yl or a methylpiperidin-4-yl;

R'''_6 is a hydroxy; a C_1–C_7-alkoxy; a carboxy which is free or esterified by a C_1–C_7-alkyl or by a benzyl;

R_7 is a C_1–C_7-alkyl;

R_8 and R_9 are each independently a hydrogen, a C_1–C_7-alkyl or a benzyl; R_9 can also be a C_1–C_7-acyl; a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7; a phenoxycarbonyl; a benzoyl; a phenacetyl; a carbamoyl which is unsubstituted or substituted by a phenyl or one or two C_1–C_4 alkyls;

m is 1, and its salts.

* * * * *